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Abstract: Resistant hypertension is defined as failure to lower blood pressure to target when a patient adheres to the maximum tolerated doses of three antihypertensive drugs including a diuretic. Notwithstanding the wide availability of several antihypertensive agents and the continued recommendation of dietary and lifestyle modifications, the prevalence of resistant hypertension remains high and is expected to increase thus underscoring the need for potential new treatment modalities in resistant hypertension. Endothelin-1 is a long-lasting potent vasoconstrictor and plays a key role in cardiovascular haemostasis. Endothelin mediates its biological activity in humans through the endothelin A and B receptors. The clinical experience and the evidence for therapy with darusentan in resistant systemic hypertension are reviewed. The leading journals that publish basic science and clinical research in the area of cardiovascular diseases and PubMed were scanned. While results from early clinical studies suggested that darusentan might emerge as new treatment option in patients with resistant hypertension, results from recent studies suggests that darusentan appears unlikely to find its way in the armamentarium for treatment of resistant hypertension.

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Darusentan, a selective endothelin A (ETA) receptor antagonist, for the oral treatment of resistant hypertension

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Abstract

Background: Resistant hypertension is defined as failure to lower blood pressure to target when a patient adheres to the maximum tolerated doses of 3 antihypertensive drugs including a diuretic. Notwithstanding the wide availability of several antihypertensive agents and the continued recommendation of dietary and lifestyle modifications, the prevalence of resistant hypertension remains high and is expected to increase thus underscoring the need for potential new treatment modalities in resistant hypertension.

Objective: Endothelin-1 is a long lasting potent vasoconstrictor and plays a key role in cardiovascular haemostasis. Endothelin mediates its biological activity in humans through the endothelin A and B receptors. The clinical experience and the evidence for therapy with darusentan in resistant systemic hypertension are reviewed.

Methods: The leading journals that publish basic science and clinical research in the area of cardiovascular diseases and PubMed were scanned.

Conclusion: While results from early clinical studies suggested that darusentan might emerge as new treatment option in patients with resistant hypertension, results from recent studies suggests that darusentan appears unlikely to find its way in the armamentarium for treatment of resistant hypertension.

Keywords: Darusentan, HMR 4005, LU 135252, hypertension, endothelin antagonist

Introduction

Worldwide, the estimated number of adults with hypertension was 972 million in 2000; by 2025 the total number is expected to increase to 1.56 billion[2007, Enseleit *et al.*, 2008]. Lifestyle factors, such as alcohol and tobacco use, physical inactivity, a salt-rich diet with processed and fatty foods, build the bottom of this disease burden, which is spreading at an alarming rate from developing countries to emerging economies, such as India and China. In developed countries hypertension remained a problematic disorder, despite a functioning health-care system and several effective treatment options. Refractory (or resistant) hypertension is defined as blood pressure that is persistently higher than the goal, i. e. 130/80 mmHg in patients with diabetes mellitus or renal disease, despite prescription of three different classes of drugs, including a diuretic in adequate doses[Mancia *et al.*, 2007]. Currently available antihypertensive agents are diuretics, aldosterone-receptor blockers, beta-blockers, alpha-blockers, combined alpha- and beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), the renin-inhibitor aliskiren, calcium channel antagonists, central alpha agonists, and direct vasodilators. Currently, there are no accepted standards of care for the treatment of patients with resistant hypertension and more information is needed to determine the optimal evaluation of such patients. The evaluation includes screening for secondary causes of resistant hypertension including hyperaldosteronism, improving adherence to treatment and identification of exogenous, blood pressure elevating substances. Once, the usual initial management steps have failed, the remaining option include new agents like endothelin – antagonists.

Yanagisawa reported the isolation, purification, and characterization of ET-1 from the culture supernatant of bovine aortic endothelial cells in 1988[Yanagisawa *et al.*,

1988]. The early observation that ET-1 is a long lasting and 5 times more potent vasoconstrictor compared to angiotensin II, quickly established its importance as a major regulator of blood pressure[Yanagisawa *et al.*, 1988, Kiowski *et al.*, 1991]. This was the most striking effect of endothelin described at the time of its isolation, and its discovery was rapidly followed by the recognition that ET-1 has a major role in the pathogenesis of a variety of cardiovascular diseases. Hence, four structurally similar isopeptides (ET-1, ET-2, ET-3 and ET-4) exist, ET-1 mediates fundamental cellular processes, such as cell proliferation[Janakidevi *et al.*, 1992, Yang *et al.*, 1999], fibrosis[Guarda *et al.*, 1993] and inflammation[Ruetten *et al.*, 1997], in human cardiovascular physiology[Boulanger *et al.*, 1990] and pathophysiology[Dohi *et al.*, 1992]. Endothelin mediates its biological activity in humans through the endothelin receptors A and B (ET-A, ET-B)[Seo *et al.*, 1994], which are members of the heptahelical G-protein-coupled receptor superfamily. The biology of endothelin and its receptors is reviewed in detail by Lüscher et al.[Luscher *et al.*, 2000], Motte et al.[Motte *et al.*, 2006] and Kirkby et al[Kirkby *et al.*, 2008]. However, the major involvement of ET-1 in various pathologic conditions, lead to the development of different endothelin receptor antagonists (ERAs) in recent years. The first approved ET-antagonist was the dual ET-A/B endothelin receptor antagonist bosentan. Most preclinical and clinical studies have been conducted in the field of CHF and pulmonary hypertension, more recent research focused on ERAs as treatment option in resistant hypertension[Enseleit *et al.*, 2008, Prasad *et al.*, 2009].

Endothelin receptor antagonism

Endothelin-1 (ET-1) plays an important role in various physiological and pathophysiological states, especially in the regulation of vascular tone. Compared to normal state, circulating plasma ET-1 levels are elevated in atherosclerosis, arterial

hypertension, heart failure and pulmonary arterial hypertension[Opitz *et al.*, 2008]. The two distinct receptor subtypes ET-A and ET-B mediate the downstream effects of ET-1. Human ET-A and ET-B bind ET-1 with equal affinity[Kirkby *et al.*, 2008]. Endothelin receptor antagonists (ERAs) have been classified as selective for the ET-A or ET-B receptor or non-selective ET-A / ET-B receptor antagonists. Endothelin receptors have been identified in numerous tissues including lung, heart, kidney, intestine, adrenal gland, eye and brain, whereas the density of binding sites is especially high in heart and lung[Simonson *et al.*, 1990]. In systemic and pulmonary vessels, ET-A receptors are located primarily on vascular smooth muscle cells (VSMCs)[Maclean *et al.*, 1994], while ET-B receptors are expressed on endothelial cells[Ogawa *et al.*, 1991] and VSMCs[Davenport *et al.*, 1993]. While both ET receptors mediate vasoconstriction and cell proliferation, endothelial ET-B receptors activate the release of vasodilating and anti-proliferative endothelium-derived substances, such as prostacyclin or nitric oxide[Motte *et al.*, 2006]. Due to these pathophysiological considerations, selective ET-A blockade may be superior over combined ET-A/B receptor blockade. However, recent data derived from cultured transfected cell lines suggest that ET-A and ET-B receptors can form constitutive heterodimers (dimerization theory)[Opitz *et al.*, 2008, Watts, 2010], which means that ET-B receptors in heterodimers may mediate vasoconstriction similar to ET-A receptors[Gregan *et al.*, 2004, Opitz *et al.*, 2008]. Furthermore, it has been hypothesized that a selective blockade of one ET-receptor may result in compensation via the unblocked receptor (cross talk)[Opitz *et al.*, 2008]. However, whether this translates into clinical benefit in systemic hypertension is still under debate, since randomized clinical trials comparing ET-A vs. ET-A/B receptor antagonism in heart failure or systemic hypertension are missing.

Chemistry

Knoll AG (Germany) developed darusentan (LU 135252, HMR 4005) was a (+)-(S)-2-(4,6-Dimethyoxy-pyrimidine-2-yloxy)-3-methoxy-3,3-diphenyl-propionic acid and its properties were first described in 1995[Raschack *et al.*, 1995]. Chemically, it is a slightly water-soluble molecule with a molecular weight of 410 g/mol (**Figure 1**). Darusentan is a selective endothelin-A (ET-A) receptor antagonist, which binds with a K_i of 1.4 nM to the ET-A receptor and a K_i of 184 nM to the human ET-B receptor, respectively. The drug is orally bioavailable, reaching peak plasma concentrations 1 hour after oral application and has a mean elimination half life time of 12.5 hours, making it suitable for once daily dosing[Cernacek *et al.*, 1998]. Darusentan is primarily metabolized in the liver and excreted via the bile, whereas urinary excretion is less than 5%[Cernacek *et al.*, 1998]. Darusentan is an experimental drug that is not yet on the market.

Studies in Heart Failure

Three phase II studies in patients with congestive heart failure have been completed and published[Spieker *et al.*, 2000, Luscher *et al.*, 2002, Anand *et al.*, 2004]. Notwithstanding darusentan improved hemodynamics acutely[Spieker *et al.*, 2000] and after three weeks of treatment in chronic heart failure in the HEAT trial[Luscher *et al.*, 2002], it did not change LV remodelling over the course of 6 months in EARTH[Anand *et al.*, 2004]. While HEAT and EARTH had been powered for hemodynamics and LV remodelling, respectively, but not for morbidity or mortality, a trend for fluid retention and related events was associated particularly with the 300 mg dose.

Studies in Hypertension

In view of the potent pressor effects of ET-1, systemic hypertension was early recognized as target for ET antagonism[Schrader *et al.*, 1990]. Moreover, circulating ET-1 concentration is elevated in patients with essential hypertension[Saito *et al.*, 1990]. One-kidney one clip (1-K 1C) Goldblatt hypertensive rats exhibit a mild degree of vascular overexpression of endothelin-1[Sventek *et al.*, 1996], but combined ET-A/B antagonism with bosentan did not cause any lowering of blood pressure after two weeks treatment[Li *et al.*, 1996]. In another study, darusentan lowered blood pressure by 20 mmHg ($p<0.01$) in DOCA-salt hypertensive rats[Li *et al.*, 1998], improved endothelial dysfunction in salt-sensitive Dahl rats[Barton *et al.*, 1998] and prevented vascular dysfunction and hypertension induced by 11β-hydroxysteroid dehydrogenase inhibition[Ruschitzka *et al.*, 2001]. Since combined ET-A/B antagonism may block both smooth muscle vasoconstrictor ET-A and ET-B receptors and endothelial vasorelaxant ET-B endothelin receptors, the possibility exists that a endothelin receptor antagonist which blocks both receptor subtypes may be less effective than a selective ET-A endothelin receptor antagonist. This could possibly account, for example, for the failure of chronically applied bosentan to lower blood pressure in spontaneously hypertensive rats[Schiffrin *et al.*, 1995, Schiffrin *et al.*, 1995], in contrast to the effect of acute intravenous infusion of an ET-A receptor antagonist[Bazil *et al.*, 1992]. Moreover, ET-1 plays a role in atherosclerosis, inflammation[Kowala *et al.*, 1995] and diabetes[Schneider *et al.*, 2002]. Hence, selective endothelin – antagonism with ET-A selective BQ-123 can reduce blood pressure in patients with chronic kidney disease and this effect is synergistic with ACE-inhibition[Goddard *et al.*, 2004] and abolished by ET-B blockade. Furthermore, ET antagonism may produce favourable renal hemodynamic changes that reduce proteinuria in patients with renal disease[Dhaun *et al.*, 2006]. However, the first large

clinical trial randomized 293 patients with mild – to – moderate essential hypertension to four doses of bosentan, enalapril or placebo[Krum *et al.*, 1998]. After 4 weeks of treatment, the combined ET-A/B receptor antagonist bosentan (500 mg QD) lowered blood systolic and diastolic pressure by 8.4±1.7 mmHg and 5.7±1.0 mmHg, respectively. This was comparable to enalapril 20 mg QD[Krum *et al.*, 1998]. Subsequently, three large clinical trials with the ET-A selective endothelin antagonist darusentan in systemic hypertension have been fully reported[Nakov *et al.*, 2002, Black *et al.*, 2007, Weber *et al.*, 2009], while the preliminary results of recently finished DORADO-AC study have only been reported as press release[2009].

The aim of the double – blind, placebo – controlled, randomized HEAT – 2 (HEAT-HTN) study was to assess the blood pressure lowering effect of three different dosages of darusentan versus placebo[Nakov *et al.*, 2002]. After discontinuation of antihypertensive medication and a 2-weeks placebo run-in period, patients were randomized to 6-weeks treatment with 10 mg, 30 mg or 100 mg darusentan once daily or placebo. A subsequent placebo withdrawal period completed the study. Office blood pressure was measured at weekly intervals. Between February 1999 and April 2000 a total of 611 patients were enrolled in 56 centres in Germany and Israel. 219 patients discontinued the study during the run – in period, primarily due to insufficient blood pressure reduction, adverse event or withdrawal of consent. After an initial increase of blood pressure during the placebo run – in phase, blood pressure markedly decreased after the first week of therapy. After adjustment for baseline blood pressure, study site and after subtraction of placebo mean change, systolic and diastolic blood pressure decreased significantly in all active treatment groups (**Table 1**)[Nakov *et al.*, 2002]. Importantly, no effect on heart rate, reflecting activation of reflex neurohumoral mechanisms, was observed throughout the study. The adverse event profiles of the 10 mg and 30 mg dosage groups were similar to

the placebo group, whereas patients in the 100 mg group experienced more adverse events, headache, flushing and peripheral oedema in particular. This study demonstrated for the first time, that treatment with darusentan in patients with moderate hypertension is effective and the blood pressure reduction was dose dependent.

The other phase II study, the DAR-201 trial was a double - blind, randomized, placebo – controlled trial in patients with resistant hypertension as defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7)[Chobanian *et al.*, 2003]. The study was conducted between July 2004 and July 2005 in 30 investigative centres in the US[Black *et al.*, 2007]. After completing of a 2-week single – blind placebo run – in phase, eligible patients were randomized in a 2:1 fashion to increasing dosages of darusentan or placebo. Darusentan was initiated at a dosage of 10 mg/d and titrated every 2 weeks at doses of 50, 100 and 150 mg/d until reaching a maximum of 300 mg/d. One blinded dose maintenance or reduction was allowed, if patients did not tolerate up – titration. Importantly, adjustment of background antihypertensive therapy was not allowed. A total of 115 patients were randomized (darusentan n = 76, placebo n = 39)[Black *et al.*, 2007]. 61% of patients had comorbid diabetes mellitus, coronary artery disease or both. 93% of the patients were on ACE-I / ARBs, 67% of patients were on calcium channel blockers, 47% were on beta-blockers and all patients were treated with a diuretic. After 10 weeks treatment, up – titration to 300 mg/d could be performed in 78% of patients. The placebo – corrected systolic blood pressure was reduced by 11.5 ± 3.1 mmHg ($p = 0.015$), while the diastolic blood pressure was reduced by 6.3 ± 2.0 mmHg ($p=0.002$) (**Table 2**). Ambulatory blood pressure measurements revealed a placebo – corrected lowering of systolic and diastolic blood pressure by 9.2 ± 2.2 mmHg and 7.2 ± 1.6 mmHg ($p < 0.001$),

respectively[Black *et al.*, 2007]. Heart rate was unaffected by treatment with darusentan, compared to baseline (0.4 ± 0.9 bpm and 2.3 ± 1.3 bpm, respectively). Reduction in blood pressure was maintained over 24 hours with a trough – to – peak ratio of 96%. The most common adverse events in the darusentan group were peripheral oedema (17%), followed by headache (11%) and sinusitis (8%).

To date, two Phase III clinical trials in patients with resistant hypertension are completed. The DORADO trial (ClinicalTrials.gov Identifier: NCT00330369, Protocol DAR-311) screened 718 patients in 117 centers in North and South America, Europe, New Zealand, and Australia. 379 patients were enrolled and randomized, however, 348 patients completed the 14-week treatment period[Weber *et al.*, 2009]. Patients were randomized to 50 mg, 100 mg and 300 mg darusentan QD or placebo. The co-primary endpoints of the study are changes from baseline to week 14 in trough sitting systolic and diastolic blood pressure. Importantly, this was a study on top of modern therapy for resistant hypertension (≥ three drugs, including a diuretic). All three darusentan dosages reduced systolic and diastolic blood pressure significantly ($p<0.0001$), **Figure 2**[Weber *et al.*, 2009]. While the mean office blood pressure (systolic/diastolic) decreased by 18/10 mmHg in the verum group, it decreased by 9/5 mmHg in the placebo group. Ambulatory blood pressure decreased by 9/8 mmHg in the darusentan group and 1/1 mmHg in the placebo group. However, there was no evidence for a significant dose response. The blood pressure goal (<140 mmHg or < 130 mmHg in patients with diabetes or chronic kidney disease) was achieved in 27% of patients in the placebo group, 53% in the 50mg group ($p=0.0002$), 53% in the 100mg group ($p<0.0001$) and 48% in the 300mg group ($p=0.0007$)[Weber *et al.*, 2009]. Adverse events were mainly related to oedema and / or fluid retention, these events occurred in 14% of patients in the placebo group, 25% in the 50mg group,

32% in the 100mg group and 25% in the 300mg group. Most of these events occurred during the first six weeks of treatment, 2% of the patients had to discontinue the study for this reason. However, six patients had serious adverse cardiac events during the trial. One sudden death occurred in the placebo group, two patients suffered from non-ST segment myocardial infarction (1 in the 50mg group, 1 in the 100mg group) and were associated with fluid retention and heart failure. In two patients in the 300mg group fluid retention and heart failure were noticed and one patient in the 100mg group hat atrial fibrillation with symptoms of heart failure[Weber *et al.*, 2009].

In the DORADO-AC study (ClinicalTrials.gov Identifier: NCT00389779, Protocol DAR-312) the blood pressure lowering effect of three different doses of darusentan (50 mg, 100 mg and 300 mg QD) was compared to 1mg guanfacine QD and placebo. Between September 2006 and August 2009, the study enrolled 849 patients with resistant hypertension. The co-primary endpoint is the same like in the Protocol DAR-311. The preliminary results were released to the public in a press release on December 14th, 2009[2009]. Gilead Science, the sponsor of the trial reported that darusentan failed to achieve the co-primary endpoint (changes from baseline to week 14 in trough sitting systolic and diastolic blood pressure)[2009]. Although the study was 95% powered to detect an 8 mmHg improvement in systolic and diastolic blood pressure, reductions in mean trough sitting systolic and diastolic blood pressures were not statistically different between darusentan and placebo groups[2009, Enseleit *et al.*, 2010]. However, darusentan demonstrated superiority in sitting systolic and diastolic blood pressure when compared to the active comparator guanfacine after 14 weeks of treatment[Enseleit *et al.*, 2010]. As a result, the extension – protocols (DAR-311-E or DAR-AC-E) that were designed to study long-

term safety and efficacy of darusentan in resistant hypertension in patients that have completed the DAR-311 or the DAR-312 protocol, were terminated prematurely.

Safety of darusentan

Although endothelin receptor antagonists have an acceptable safety profile, side effects are relatively common. Indeed, in the HEAT-HTN study 116 (29.6%) of the 392 patients randomized discontinued the study mainly for lack of treatment effect (insufficient blood pressure reduction) or occurrence of adverse events. The most frequent reported clinical adverse events of the treatment with darusentan seem to be related to non-specific vasodilating effects and include headache, dizziness, nausea, peripheral oedema and nasal congestion[Sütsch *et al.*, 1998, Spieker *et al.*, 2000, Luscher *et al.*, 2002, Packer *et al.*, 2002, Anand *et al.*, 2004]. While the incidence of peripheral oedema or fluid retention was observed in up to 27% of the darusentan group (vs. 14% in the placebo group) in the trial by Weber et al.[Weber *et al.*, 2009], the exact pathophysiological mechanism remains still elusive. Indeed, darusentan causes a decrease in blood pressure by a vasoconstrictor blockade, leading to peripheral vasodilatation an oedema, as observed with the vasodilatating dihydropyridine calcium channel blockers. This is underscored by the finding that glomerular filtration rate remained unaffected by treatment[Weber *et al.*, 2009, Williams, 2009]. It may be aggravated by dual ERAs due to the reported ET-B mediated down-regulation of the epithelial sodium channel in the renal tube[Plato *et al.*, 1999]. However, in clinical trials incidence of fluid retention as an adverse event has not been reported differently with selective ET-A vs. combined ET-A/B receptor antagonists[Motte *et al.*, 2006].

Liver toxicity is an often-reported dose – dependent adverse effect during treatment with ERAs. This effect appears to be related to impaired bile salt transport, causing

accumulation of toxic bile salts in hepatocytes[Fattinger *et al.*, 2001]. The safety database of the bosentan trials revealed that liver toxicity occurs early as well as late in treatment in 2-18% of patients[Fattinger *et al.*, 2001]. Active surveillance of liver function in patients treated with ERAs prevents clinical significant hepatitis but may lead to discontinuation of therapy in 5% of treated patients at one year[Motte *et al.*, 2006]. The “Research on Endothelin Antagonism in Chronic Heart Failure” (REACH-1) trial[Packer *et al.*, 1998], was terminated prematurely because of a reversible increase in concentrations of liver aminotransferases. However, at haemodynamically effective doses, darusentan did not show significant elevatation of hepatic enzymes in dose-finding studies[Spieker *et al.*, 2000, Luscher *et al.*, 2002].

Due to teratogenicity, ERAs are contraindicated during pregnancy and animal models revealed that the endothelin system appears to play an important role in fetal development[Treinen *et al.*, 1999]. Mice knocked out for the ET-A receptor[Clouthier *et al.*, 1998] develop lesions that resemble those seen in the CATCH22 syndrome in humans, which include severe craniofacial deformities, defects in the cardiovascular outflow tract, thymic hypoplasia and cleft palate[Wilson *et al.*, 1993]. ET-B receptor deficient mice develop white spotted coats and aganglionic megacolon, the same pathological phenotype as observed in Hirschsprung disease[Hosoda *et al.*, 1994]. In CHF, ET – antagonism was associated with a trend towards more adverse events (including death) with higher doses, in particular.

Darusentan for the Treatment of Resistant Hypertension

While human ET-A and ET-B receptors bind ET-1 with equal affinity, endothelin receptor antagonists have been classified as selective for the ET-A or ET-B receptor or as non-selective, combined ET-A/B receptor antagonists[Kirkby *et al.*, 2008, Enseleit *et al.*, 2010]. The ET-A:ET-B binding ratio of the ET-A receptor antagonist

BQ-123, of 2000:1 in a standard *in vitro* assay, is considered the benchmark to classify the selectivity of different ETAs[Dupuis, 2000, Goddard *et al.*, 2004]. However, darusentan is a borderline selective ET-A receptor antagonist with a relative ET-A/B selectivity of 170:1[Neuhofer *et al.*, 2009] and the selectivity for ET-A receptors is affected by the dose of the antagonist[Goddard *et al.*, 2002, Dhaun *et al.*, 2010]. This may explain the very flat or even absent dose-response of darusentan in recent trials in patients with resistant hypertension[2009, Weber *et al.*, 2009]. The effect of an ETA on plasma ET-1 levels *in vivo* is considered an indicator of functional selectivity. Since ET-B receptors play a role in clearing ET-1, decreasing ET-1 levels after treatment with an ET-antagonist suggests selectivity, because ET-B receptors remain functional[Opitz *et al.*, 2008]. To further elucidate the ET-receptor selectivity of darusentan, plasma levels of ET-1, an established biomarker of ET-receptor blockade[Goddard *et al.*, 2004], should be reported.

Early clinical phase II studies suggested that darusentan might find a place in the treatment of resistant hypertension[Enseleit *et al.*, 2008, Enseleit *et al.*, 2010]. However, the missing dose-dependency of darusentan in the recently published study by Weber et al.[Weber *et al.*, 2009] and the preliminary negative results of the DORADO-AC study cast doubt on the concept of ET-antagonism in resistant hypertension. Although data regarding the secondary end points and the safety of darusentan have not yet been released, darusentan (and with it most likely the whole class of ET-A antagonists) appears unlikely to find its way into our armamentarium for the treatment of resistant hypertension[Enseleit *et al.*, 2010].

Conclusion

As the selective ET-A antagonist darusentan reduced blood pressure by acting through a new pharmacological pathway that had not previously been the target of

oral antihypertensive drugs, this may permit to achieve blood pressure control in patients, who are difficult to treat and who are at increased vascular risk, e. g. patients with diabetes mellitus. While, early clinical results from phase II studies suggest, that darusentan may find a place in the treatment of resistant hypertension, more recent phase III studies could not find a dose-dependent blood pressure reduction. Indeed, the DORADO-AC study failed to achieve its co-primary efficacy endpoint (changes from baseline to week 14 in trough sitting systolic and diastolic blood pressure), and the sponsor of the trial, Gilead Science, announced to terminate the further development of darusentan for the treatment of resistant hypertension.

Conflict of interest

The authors have no conflict of interest in connection with this manuscript.

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Table 1: HEAT-2: Placebo – subtracted mean change from baseline. Results are adjusted for baseline and study centre. For systolic and diastolic blood pressure, the last value under double – blind treatment was used for each individual. The confidence interval was adjusted for baseline blood pressure and centre, but not for multiple testing. Modified from Nakov et al[Nakov *et al.*, 2002].

	Systolic blood pressure			Diastolic blood pressure		
	Mean [mmHg]	95 % CI [mmHg]	p	Mean [mmHg]	95 % CI [mmHg]	p
100 mg	-11.3	-16.3; -6.2	0.0001	-8.3	-11.1; -5.5	0.0001
30 mg	-7.3	-12.3; -2.4	0.004	-4.9	-7.7; -2.2	0.0005
10 mg	-6.0	-11.0; -0.9	0.02	-3.7	-6.6; -0.9	0.009

Table 2: Comparison of office blood pressure lowering efficacy of darusentan and bosentan in patients with hypertension. *No standard deviation provided in publication.

Drug	Dose	ET – Antagonism	Systolic BP Reduction (mmHg)	Diastolic BP Reduction (mmHg)
Bosentan[Krum *et al.*, 1998]	500 mg QD	A / B	8.4±1.7	5.7±1.0
Darusentan[Nakov *et al.*, 2002]	100 mg QD	A	11.3*	8.3*
Darusentan[Black *et al.*, 2007]	300 mg QD	A	11.5±3.1	6.3±2.0
Darusentan[Weber *et al.*, 2009]	300 mg QD	A	18±19	10±11

Figure 1: Chemical structure of darusentan.

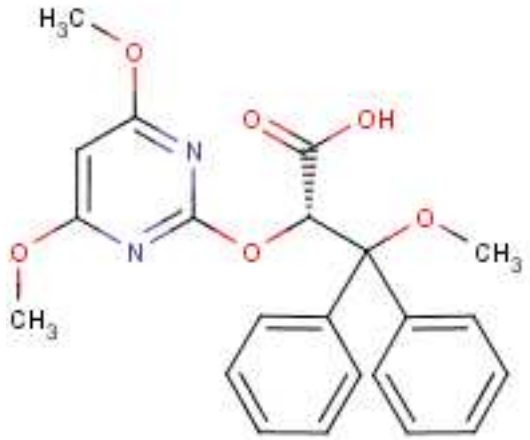

Figure 2: Changes from baseline in mean 24-h ambulatory blood pressure after 14 weeks. (A) Change in systolic blood pressure (SBP). (B) Change in diastolic blood pressure (DBP). Error bars show SE. *p=0·0002. †p<0·0001, adapted from [Weber *et al.*, 2009]